

## Calorimetric studies on two halogenated uracil isomers



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### ABSTRACT

The heat capacities of 6-chlorouracil and 5-chlorouracil isomers were measured using a Quantum Design physical properties measurement system (PPMS) based on a heat pulse relaxation method over the temperature range from (1.9 to 300) K, and the experimental data were fitted as a function of temperature using a series of theoretical and empirical models for the appropriate temperature ranges. The results of these fits were used to calculate thermodynamic function values,  $C_{p,m}^0$ ,  $\Delta_0^T S_m^0$ , and  $\Delta_0^T H_m^0$  from  $T = (0.5 \text{ to } 300)$  K. The standard molar heat capacities, entropies and enthalpies of 6-chlorouracil and 5-chlorouracil at 298.15 K and 0.1 MPa were determined to be  $C_{p,m}^0 = (136.94 \pm 1.37) \text{ J K}^{-1} \text{ mol}^{-1}$  and  $(137.95 \pm 1.38) \text{ J K}^{-1} \text{ mol}^{-1}$ ,  $S_m^0 = (156.87 \pm 1.57) \text{ J K}^{-1} \text{ mol}^{-1}$  and  $(154.97 \pm 1.55) \text{ J K}^{-1} \text{ mol}^{-1}$  and  $H_m^0 = (23.01 \pm 0.23) \text{ kJ mol}^{-1}$  and  $(23.07 \pm 0.23) \text{ kJ mol}^{-1}$ , respectively.

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### 1. Introduction

As an important part of RNA, uracil commonly exists in living organisms and is widely used in medicine and biochemical research fields. 5-chlorouracil and 6-chlorouracil, shown in Scheme 1, are two important halogen derivatives of uracil for pharmaceutical synthesis due to their low toxicities, unique biological activities and good internal absorptions. [1] For example, 5-chlorouracil has a similar structure with thymine, which can replace the thymine in DNA, and therefore it can be used in the synthesis of antineoplastic and anti-inflammatory drugs with antimetabolic functions. [2] 6-chlorouracil is usually employed as a pharmaceutical intermediate in synthesizing diabetes drugs. [3] To better understand the synthesis process and properties of these halogen derivatives, [4,5] their thermodynamic properties should be further investigated.

Calorimetry is a classic subject that has an important status in natural science and other related fields. The thermodynamic properties of these drug intermediates play a crucial role in the field of drug synthesis and development by helping researchers predict reaction trends and design reasonable synthetic routes. A number of thermodynamic properties of uracil and its derivatives have already been reported in literature. For example, Zielenkiewicz et al., [6] measured the partial molar heat capacity of alkylated uracil in water at 298.15 K and found that the heat capacity value could increase by increasing the number of methylene groups

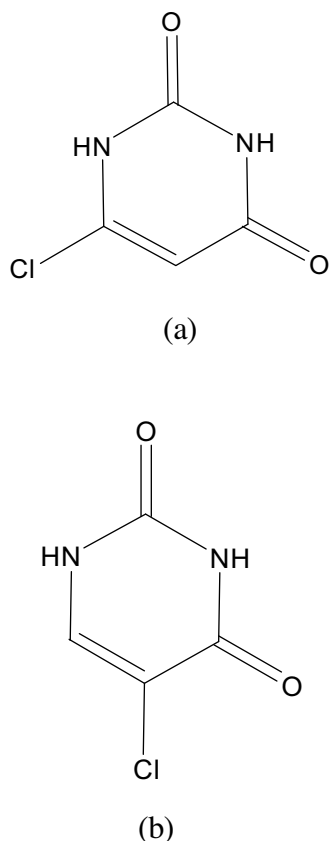
attached to the diketopyrimidine ring. Also, Zielenkiewicz et al. [7] determined the molar heat capacity of solid uracil, its alkylated and halogenated derivatives, and cyclooligomethylenouracils in the temperature range of (298.15–343.15) K using a differential scanning calorimeter.

As for other uracil derivatives, their heat capacities are generally estimated by correcting the contributions of C–CH<sub>3</sub>, N–CH<sub>3</sub>, and C–NO<sub>2</sub> groups as well as F, Cl, Br, and I atoms to the total heat capacity at 298.15 K using Chickos' method of heat capacity calculations. Chickos' method was developed for providing heat capacity estimation of the condensed phase with a standard error of  $19.5 \text{ J mol}^{-1} \text{ K}^{-1}$  and  $26.9 \text{ J mol}^{-1} \text{ K}^{-1}$  for the 810 liquids and 446 solids used in this study as a data base, respectively. [8] Zielenkiewicz et al. [6] and Chickos et al., [9] found that Chickos' method could not distinguish the substituted position in the methyl-substituted uracil derivatives. However it could distinguish the substituted positions in halogen-substituted and alkyl chain- or ring-substituted uracil derivatives. Although Zielenkiewicz's work involved heat capacity experimental studies, there is no report on heat capacity measurements on 5-chlorouracil and 6-chlorouracil over a relatively broad temperature region.

In this work, the low temperature heat capacities of 6-chlorouracil and 5-chlorouracil have been measured using a Quantum Design physical properties measurement system (PPMS) based on a heat pulse relaxation method over the temperature range from (1.9 to 300) K. On the basis of the curve fitting of the experimental heat capacities, the thermodynamic functions of these isomers have been calculated. Moreover, the heat capacity difference between 6-chlorouracil and 5-chlorouracil has also

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**Scheme 1.** The molecular structure of (a) 6-chlorouracil and (b) 5-chlorouracil.

**Table 1**  
Sample information of 6-chlorouracil and 5-chlorouracil.

| Name           | CAS No.   | Source | $M_r^a$ | $X^b$ |
|----------------|-----------|--------|---------|-------|
| 6-Chlorouracil | 4270–27-3 | Meryer | 146.53  | 0.99  |
| 5-Chlorouracil | 1820–81-1 | Meryer | 146.53  | 0.99  |

<sup>a</sup> The value of  $M_r$  is based on the most recent set of relative atomic masses recommended by IUPAC.

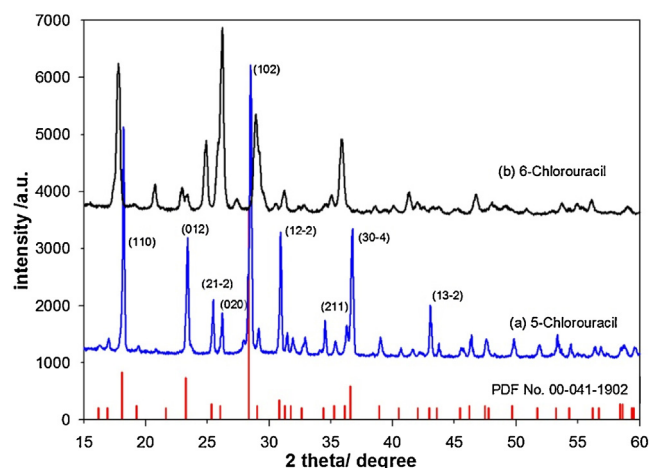
<sup>b</sup> Purity in moles fraction claimed by manufacturer.

been discussed and explained from the viewpoint of their different molecular structures.

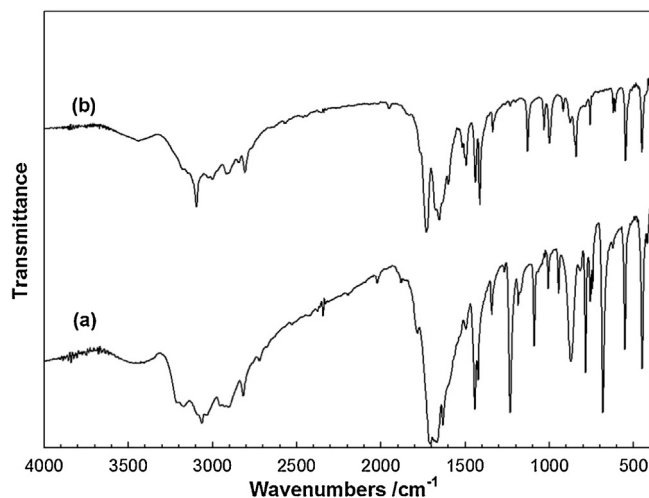
## 2. Experimental

5-Chlorouracil, shown in Scheme 1, has a similar structure with 6-chlorouracil other than the chlorine atom substituted position. The sample information for the two isomers used in the calorimetric measurement is given Table 1. These samples were purchased from Meryer (Shanghai) Chemical Technology Co., Ltd. with a mass purity better than 0.99. The purity and crystallinity of two samples were further verified by a powder X-ray diffraction technique using a Cu  $K_\alpha$  radiation (0.15418 nm) (PANalytical Co. X'pert PRO, Netherlands) operated under a voltage of 40 kV and a current of 40 mA. The high-purity copper foil from Alfa Aesar Corporation (Product No. 10950) used for the sample preparation in the heat capacity measurement is 0.025 mm thickness with a mass fraction purity of 0.99999.

The XRD results, presented in Fig. 1, show that the diffraction peaks of 5-chlorouracil are well consistent with the standard patterns (PDF card No. 00-041-1902) from International Centre for Diffraction Data, indicating that this sample exhibits good crystallinity and is phase pure (Fig. 1). Unfortunately, we were not able



**Fig. 1.** The standard and experimental x-ray diffraction (XRD) patterns of (a) 5-chlorouracil, and experimental XRD patterns of (b) 6-chlorouracil.



**Fig. 2.** Experimental FT-IR spectra of (a) 5-chlorouracil and (b) 6-chlorouracil. The FT-IR measurement were performed from 400 to 4000  $\text{cm}^{-1}$  on a Bruker EQUINOX 55 instrument using the KBr technique with 1 mg sample per 300 mg KBr.

to find the standard XRD patterns of 6-chlorouracil in the related database we could access, but from the collected patterns in Fig. 1 it can be seen that 6-chlorouracil is crystalline. To confirm the phase purity of 6-chlorouracil, we measured the FT-IR spectra of these two isomers using a Bruker EQUINOX 55 instrument, and from the results (Fig. 2, supplemental materials) it can be seen that the recorded spectra of 6-chlorouracil is in good agreement with the standard FT-IR spectra (No.51693) from Spectral Data Base (SDBS) showed in Fig. S1 of supplemental materials.

The heat capacity measurements of 6-chlorouracil and 5-chlorouracil were conducted on a PPMS over the temperature range of (1.9 to 300) K. The temperature intervals during the measurements were set to have a logarithmic space below 100 K and have a spacing of 10 K intervals above 100 K. The accuracy of heat capacity measurements using our PPMS were found to be within  $\pm 3\%$  in the temperature range from (1.9 to 20) K and  $\pm 1\%$  in the range from (20 to 400) K, by measuring the heat capacities of calorimetric standard materials of copper pellet,  $\alpha\text{-Al}_2\text{O}_3$  and benzoic acid recommended by National Institute of Standard and Technology. [10] The sample preparation for the heat capacity measurements was the same as the technique developed by Shi et al., [11,12] for powdered sample measurement using a PPMS calorimeter. The detailed sample preparation process can be found in literature. [11,12] In general,

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